Neural circuit dysfunction in mouse models of neurodevelopmental disorders

Isabel del Pino[1,†], Beatriz Rico[1,2,*] and Oscar Marín[1,2,*]

Address

[1]Centre for Developmental Neurobiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE1 1UL, United Kingdom

[2]MRC Centre for Neurodevelopmental Disorders, King's College London, London SE1 1UL, United Kingdom

[†]Present address: Neurocentre Magendie INSERM U1215, 33077 Bordeaux, France

*Corresponding authors: Beatriz Rico (beatriz.rico@kcl.ac.uk) or Oscar Marín (oscar.marin@kcl.ac.uk)

Summary

Neuropsychiatric disorders arise from the alteration of normal brain developmental trajectories disrupting the function of specific neuronal circuits. Recent advances in human genetics have greatly accelerated the identification of genes whose variation increases the susceptibility for neurodevelopmental disorders, most notably for autism spectrum disorder (ASD) and schizophrenia. In parallel, experimental studies in animal models – most typically in mice – are beginning to shed light on the role of these genes in the development and function of specific brain circuits. In spite of their limitations, understanding the impact of pathological gene variation in animal models at the level of specific neuronal populations and circuits will likely contribute to orienting human clinical studies in the search for precise disease mechanisms and novel treatments.

Introduction

Our understanding of the etiology of psychiatric disorders has increased exponentially over the last decade due to massive advances in human genetics and epidemiology studies. These studies suggest that neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia are highly polygenic, with pleiotropic risk alleles and a complex background of gene-environment interactions underlying the pathophysiology. In this puzzling scenario, where genetic risk and pathogenic mechanisms overlap across multiple conditions [1], an emerging hypothesis is that unrelated genetic abnormalities may lead to similar psychiatric disturbances by altering the function of the same brain circuits. In addition, it has been proposed that neurodevelopmental disorders may primarily segregate by the timing when brain development deviates from a normal trajectory [2,3].

Research on animal models of neurodevelopmental disorders is also progressively shifting from an almost exclusive focus on behavior to the identification of neural circuit alterations linked to specific behavioral traits in an attempt to isolate etiological mechanisms that explain specific symptomatology [4]. Most of these studies concentrate on the analysis of genes whose variation has highly penetrant effects in humans, such as those linked to syndromic conditions, which illustrate the difficulties that exist in the field for the modeling of complex genetic variation. Here, we review recent work on animal models of neurodevelopmental disorders that point to converging defects in brain circuits across multiple conditions. This dissection of specific neural circuit dysfunctions largely concentrates on the analysis of genes linked to autism spectrum disorders (ASD) and schizophrenia. Whenever possible, emphasis is made on the impact of gene variation on developmental trajectories, as opposed to concentrating on the analysis of adult phenotypes.

Cortical circuits

Functional deficits in long-range cortico-cortical circuits are though to be implicated in the pathophysiology of several neurodevelopmental disorders (Figure 1). For example, cognitive dysfunction is common in schizophrenia and has been associated with deficits in functional connectivity between the hippocampus and the prefrontal cortex (PFC) [5,6]. Consistently, mice modeling a human microdeletion (22q11.2), a well known genetic risk factor for schizophrenia, have profound deficits in the synchronization of PFC and hippocampal networks during working memory demands [7]. Recent work has shown that these defects are likely due to the deficient growth of pyramidal cell axons in the PFC at perinatal stages [8]. Notably, these functional alterations can be rescued by interfering with the signaling cascades controlling axonal growth during early development [8,9].

Functional magnetic resonance imaging (MRI) has also consistently identified disturbances in cortico-cortical circuits in ASD patients. In particular, it is suggested that long-range connectivity is reduced in the neocortex, while local connectivity is enhanced [10]. Recent studies in animal models carrying loss of function alleles for genes linked to syndromic forms of autism have demonstrated comparable defects. Mutations in *CNTNAP2*, a gene encoding the neurexin-related cell-adhesion protein Caspr2, are strongly linked to multiple neurodevelopmental conditions, including autism and epilepsy [11]. Functional MRI studies have shown that mice carrying homozygous *Cntnap2* mutations exhibit prominent deficits in functional connectivity between posteromedial cortical areas and the PFC, which are probably caused by a deficit pyramidal cells projecting to the PFC [12]. Long-range cortico-cortical connectivity also seems impaired in *Fmr1*$^{-/y}$ mice, a model of Fragile X syndrome. Diffusion tensor MRI and viral tracing experiments revealed reduced connectivity between the primary visual cortex and other cortical areas in *Fmr1*$^{-/y}$ mice compared to controls [13]. These defects likely arise during neonatal stages and are readily

evident in juvenile mice [14]. Finally, mice heterozygous for a loss of function mutation in PTEN, which encodes a protein phosphatase that regulates mTOR signalling and is linked to macrocephaly and autism, also exhibit prominent defects in long-range cortical projections. In particular, *Pten*$^{+/-}$ mice have exuberant projections from the PFC to the amygdala, a phenotype that underlies the social behavior defects observed in these mice [15]. Although this study focused on the connectivity between the prefrontal cortex and the amygdala, altered cortical connectivity is unlikely to be restricted to this circuit in *Pten*$^{+/-}$ mice. Consistent with this idea, the analysis of mice carrying duplications in the ASD-linked gene *Cyfip1* (Cytoplasmic FMR1 interacting protein 1) also revealed defective mTOR signaling and abnormal development of PFC neurons [16].

Dysfunction in long-range cortical circuits often occurs concomitantly with local-circuit alterations. Impaired homeostatic responses to perturbations of excitatory-inhibitory balance in the cerebral cortex are widespread among mouse models of neurodevelopmental disorders [17]. Mouse models of Rett syndrome, caused by loss of function mutations in the gene encoding methyl-CpG-binding protein 2 (*MECP2*), exhibit prominent defects in the organization and maturation of inhibitory circuits [18,19] and display increased susceptibility to hyperexcitability. Interestingly, *Mecp2* duplications, which are also pathogenic in humans, cause similar neural circuit abnormalities than loss of function *Mecp2* mutations [19]. Conditional deletion of *Pten*, another ASD-associated gene, also causes widespread defects in dendrites and axons tracts in the telencephalon [20], along with abnormal variation in the ratios of different classes of interneurons [21].

Cognitive deficits in schizophrenia have been linked to deficits in GABAergic interneurons at multiple levels. Human postmortem studies have identified synaptic deficits in fast spiking interneurons [22,23], a population of GABAergic cells that are involved in the modulation of gamma rhythms and working memory [24]. Consistent with these

observations, human studies have linked alterations in gamma rhythms to profound deficits in working memory performance [25-29].Recent work has shown that similar alterations are recapitulated in mice carrying mutations in the gene encoding Proline dehydrogenase (*Prodh*), which resides within the schizophrenia-linked 22q11.2 deletion, have decreased levels of GABA and specific deficits in gamma-band oscillations [30].

Synchronization of local and long-range pyramidal cell activity can result from defects in the wiring and function of specific classes of cortical interneurons. The recruitment of fast-spiking Parvalbumin-expressing (PV+) interneurons is compromised in mice carrying mutations in genes linked to autism and schizophrenia. Conditional deletion of Neuroligin-3 (NL3) from PV+ interneurons impairs the properties of excitatory input, which in turn reduces gamma oscillations and perturb behavior [31]. Similarly, conditional removal of the tyrosine kinase receptor ErbB4 from PV+ interneurons impairs the development of synaptic excitatory input and alters the balance between neuronal excitation and inhibition in cortical circuits [32]. A similar synaptic phenotype is observed when ErbB4 is deleted from CCK+ interneurons, although the behavioral consequences are very different. While perturbing the recruitment of PV+ interneurons by pyramidal cells impairs gamma oscillations and a wide range of cognitive tasks [32], deficient recruitment of CCK+ interneurons decreases theta oscillatory activity and alters spatial coding by place cells (Figure 2a–c) [33]. Interestingly, recent studies have also shown reduced spatial map stability in mice modeling the human 22q11.2 microdeletion [34], which reinforces the view that disruption of local assemblies in the hippocampus is a common feature of schizophrenia.

Defects in the formation of inhibitory synapses onto pyramidal cells have also been described in several mouse models of neurodevelopmental disorders. Cell adhesion molecules linked to neurological disease such as Neurexins and Neuregulins regulate the

synaptic output of GABAergic interneurons in a cell-specific manner. For example, complete deletion of all neurexin forms decreases dramatically the number of PV+ inhibitory synapses onto pyramidal cells [35]. Loss of *Nlgn4*, one of the most common genes whose variation has been linked to ASD, also disrupts perisomatic inhibitory synaptic neurotransmission onto pyramidal cells [36]. Conversely, deletion of ErbB4 – the receptor mediating neuregulin function in interneurons [37] – specifically impairs the formation of chandelier cell synapses [32] and CCK+ basket cells [33]. These findings suggest that each interneuron class requires specific synaptic machineries to integrate into local networks, and that defects in specific inhibitory synapses are common in neurodevelopmental disorders.

Acute manipulation of the balance between neuronal excitation and inhibition in the cerebral cortex may have therapeutical potential. For instance, decreasing the excitatory-inhibitory balance in the medial PFC in mouse models of ASD or schizophrenia (by either optogenetically increasing the excitability of inhibitory PV+ interneurons or decreasing the excitability of pyramidal cells) acutely rescues prominent deficits affecting social and cognitive domains [38,39]. Although optogenetic manipulations might be difficult to implement in humans, these experiments suggest that equivalent pharmacological interventions – provided that they achieve the desired specificity – might be beneficial in autism and perhaps other disorders. Importantly, perturbation of E/I balance early in development might destabilize neural assemblies persistently [40] through developmental plasticity mechanisms that might not be reverted by acutely restoring E/I balance. The potential of neural circuits to undergo adaptive structural rearrangements in response to environmental stimuli decreases progressively during postnatal development (Figure 2d). Therefore, therapeutic interventions directed to restore circuit dysfunction by manipulating

E/I balance are required to be timely fitted to counteract pathological developmental trajectories [2].

Striatal circuits

Restricted, repetitive patterns of behavior are among the most characteristic clinical features of ASD. As these behaviors are hallmarks of other basal ganglia-related disorders such as Tourette syndrome and obsessive-compulsive disorder (OSD), recent work on animal models of ASD has largely focused on the analysis of corticostriatal circuits. Electrophysiological studies in mice have shown that the development of corticostriatal connections occurs during a narrow postnatal period that is characterized by extensive glutamatergic synaptogenesis in striatal projection neurons and a parallel increase in corticostriatal circuit activity [41]. The functional coupling between these two areas is so efficient during this critical period that early alterations in the activity of cortical neurons may have a massive impact in the long-term configuration of corticostriatal circuits. Consistently, a mouse model of ASD carrying mutations in *Shank3* alleles exhibits cortical hyperactivity at early postnatal stages and progressively develops hyperconnectivity between cortical pyramidal cells and striatal projection neurons [41]. Interestingly, repeated hyperactivation of corticostriatal synapses induces repetitive behaviors in mice [42], which suggest that abnormal activation of corticostriatal circuits during early postnatal development may underlie the motor stereotypies that characterize multiple neurodevelopmental disorders. In agreement with this idea, ASD-linked mutations in *Shank3* seem to have an earlier impact on neural circuits than schizophrenia-linked mutations in the same gene [43] (Figure 1).

Other studies suggest that decrease activation of corticostriatal circuits during development may also cause prominent phenotypes. For instance, *FOXP2* mutations in humans are

linked to spoken language disabilities and defects in corticostriatal circuits. Mice carrying loss of function *Foxp2* alleles develop reduced numbers of corticostriatal synapses at the juvenile stage which impacts on ultrasonic vocalizations [44]. Thus, abnormal development of corticostriatal projections may have different functional implications, depending on the timing and nature of the alterations. Altogether, these studies strongly suggest that early developmental disruption of corticostriatal circuits leads to increase repetitive behavior and motor abnormalities in mice. Importantly, some of these alterations may also compromise social communication by affecting motor routines such as those required for the generation of ultrasonic vocalization.

Enhanced motor learning has been associated with the consolidation of repetitive motor routines, a prominent feature of ASD patients. Consistently, acquired motor learning is commonly increased among ASD mouse models [20,45-48]. In rotarod performance tests, for example, mice carrying ASD mutations typically outperform control mice, achieving higher levels of motor performance than controls over the same period of time [46,48]. Previous work has linked the basal ganglia with the acquisition of repetitive and stereotyped behaviors [49], but the specific neuronal circuits underlying the enhanced motor learning ability of ASD mouse models have remained unknown until recently. Several studies have now shown that neural circuit defects in the nucleus accumbens enhance the acquisition of repetitive motor behaviors in mice [46,48]. For instance, NL3 mutations associated to ASD cause defects in the inhibitory control of striatal projection neurons, through a shift in the E/I balance in D1 (dopamine receptor 1)-expressing medium spiny neurons, likely enhancing the output of this pathway [46]. Specific deletion of NL3 in the ventral striatum recapitulates the motor behavioral abnormalities observed in null NL3 mutants [46], suggesting that this region is prominently affected by the loss of NL3 function.

Heterozygous mice for a loss of function *Cdh8* allele, which encodes an ATP-dependent chromatin remodeler linked to ASD [50], also exhibit repetitive behavior [51] and enhanced motor learning in rotarod tests [48]. Although the effects of the loss of Cdh8 function in brain development are likely diverse [51,52], electrophysiological experiments have shown that medium spiny neurons in the striatum of *Cdh8*$^{+/-}$ mice received enhanced excitation and decreased inhibition, which probably contribute to increase the output of these neurons [48]. Remarkably, deletion of *Cdh8* from neurons in the core of the nucleus accumbens is also sufficient to recapitulate the motor behavioral phenotype [48]. Together, these studies link the abnormally enhanced acquisition of motor tasks that characterize mouse models of ASD with defects in ventral striatal circuits.

Neuromodulation of long-range and local circuitries

Dopamine plays a critical role in regulating social behavior and repetitive actions by modulating the activity of neurons at different levels of cortico-striatal-thalamic-cortical circuits. As such, defects in the function of dopaminergic neurotransmission have been described in multiple neurodevelopmental disorders. For instance, human studies suggest that cortical hypodopaminergia and striatal hyperdopaminergia are common in schizophrenia patients [53], and recent work have consistently reported that PV+ interneurons in mice modeling the schizophrenia-linked 22q11.2 deletion are less susceptible to modulation via D2 receptors, which disrupts the ability of these cells to influence E/I balance [54]. Interestingly, disruption of E/I balance in the cortex may in turn impact the activity of dopaminergic cells in the midbrain. In agreement with this, mice with defects in PFC neuron excitability exhibit abnormally increased striatal dopamine release [55] (Figure 1). This study provides a potential explanation for apparently unrelated observations in schizophrenia, such as loss of dendritic spines in pyramidal cells, enhanced excitation, and altered striatal dopamine.

Several lines of evidence also point to impaired dopaminergic function in reward circuits in ASD [56], which is likely caused by a decrease in the activity of midbrain dopaminergic neurons. In mice, specific loss of *Shank3* function in the ventral tegmental area leads to reduction in the activity of dopaminergic neurons that impairs social reward mechanisms [57]. These results are consistent with the analysis of mice engineered to expressed abnormally increased levels of Ube3a in the VTA, which model a common and highly penetrant form of ASD found in humans carrying 15q11-13 triplications. Overexpression of Ube3a in this region disrupts excitatory neurotransmission in glutamatergic neurons in the VTA and impairs normal social behavior [58].

Sensory circuits

Autism spectrum disorder involves deficits in sensory processing, including aberrant reactivity to sensory stimuli [59,60]. Previous work has primarily focussed on sensory responses in primary cortical areas, but recent studies in animal models of ASD have revealed that defects in sensory processing might originate from perturbations in other stations of sensory pathways. For instance, mice harboring mutations in ASD-associated genes in humans such as *Mecp2*, *Gabrb3*, *Shank3* and *Fmr1* exhibit tactile hypersensitivity that is primarily caused by a reduction of presynaptic inhibition in primary sensory neurons [61]. This suggests that at least some of the sensory alterations that characterize ASD patients are caused by circuit deficits in the spinal cord. In addition, these studies indicate that anxiety and aberrant social behaviors in ASD patients might be secondary to disruption of sensory responses.

Sensory processing defects in ASD might also be linked to defects in thalamocortical connectivity. Recent studies revealed that the function of the reticular thalamic nucleus, a structure involved in gating thalamocortical circuits, is altered in *Ptchd1*-deficient mice, a

gene mutated in some patients with ASD, intellectual disability and attention deficit hyperactivity disorder [62]. *Ptchd1* is strongly expressed in the reticular nucleus at neonatal stages, and its deletion from this structure is sufficient to replicate some of the behavioral deficits observed in humans carrying PTCHD1 mutations.

Concluding remarks

Advances in human genetics over the last decade have led to the identification of dozens of genes whose variation is associated with neuropsychiatric abnormalities, most typically in syndromic forms of ASD and other neurodevelopmental disorders. Understanding the impact of pathological gene variation in the context of neural circuit dysfunction during postnatal development is perhaps the most promising approach to increase our understanding of the etiology of these conditions. In other words, animal models have the potential to help us move from “which” (gene) to “where” (in the brain) and “when” (during development). Linking these variables should lead to the identification of critical developmental windows during which specific neural circuits are particularly sensitive to pathological insults [2]. A better understanding of pathophysiological trajectories at the level of specific neural circuits should also guide the development of new therapeutical approaches.

The analysis of neural circuit abnormalities and their associated behavioral traits reveal important differences among neurodevelopmental disorders. For example striatal hyperdopaminergia and psychosis are perhaps uniquely characteristic of schizophrenia arising relatively late in postnatal development, whereas the abnormal function of corticostriatal circuits and its impact of repetitive behaviors are more frequently associated with ASD and occur relatively early in development. Cognitive deficits, on the other hand, seem to be prevalent across a wide range of neurodevelopmental disorders. Consistent with

this idea, copy number variants conferring risk of ASD or schizophrenia also modulate cognition in healthy controls [63]. In this context, perturbation of the balance between excitatory and inhibitory neurons in the cerebral cortex, and of the mechanisms that control the homeostatic regulation of this balance, have been shown to disrupt cognition (working memory, cognitive flexibility, spatial coding, sensory perception) and appear early during development across a wide range of animal models. Thus, disruption of cortical assemblies might be a common early signature of neurodevelopmental disorders.

Acknowledgements

We are grateful to members of the Rico and Marín labs for discussions on this subject. We apologize to colleagues whose work is not cited in this review. Unfortunately, space was too limited to cite all significant original articles. Our work on this topic is supported by grants from the Initiative d'excellence de l'Université de Bordeaux (IdEX) to I.dP., the European Research Council (ERC-2012-StG 310021) and the Wellcome Trust (202758/Z/16/Z) to B.R., and the European Research Council (ERC-2011-AdG 293683), the Simons Foundation (SFARI 239766) and the Wellcome Trust (103714MA) to O.M. B.R. and O.M. are Wellcome Trust Investigators. The authors declare no conflicts of interest.

Figure legends

Figure 1. Summary of neural circuit dysfunctions in mouse models of ASD and schizophrenia during postnatal development. **(a)** Schematic showing brain regions disrupted in mouse models of autism and schizophrenia. **(b, c)** Schematics displaying brain regions and connections disrupted in mouse models of ASD (b) and schizophrenia (c). Brain regions and connections are color-matched to specific mouse strains in which defects have been reported for those areas. Chromosomal copy number variants in humans than encompass genetic mutations modeled in mice are indicated between square brackets. Arrows indicate the brain connections that have been characterized. Del, deletion; dup, duplication; trip, triplication.

Figure 2. Local microcircuits regulating excitatory/inhibitory (E/I) balance are affected in animal models of neurodevelopmental disorders. **(a)** Schematic of local microcircuits composed of cortical glutamatergic pyramidal cells (grey), GABAergic basket cells expressing cholecystokinin (CCK+, purple) and GABAergic basket as well as chandelier cells expressing parvalbumin (PV+, red). **(b)** Abnormal synchronization of hippocampal activity results from developmental disruption in E/I balance. Schematic examples of altered oscillatory activity in the low frequency (filtered LFP signal in the θ-band, upper panel) and/or high frequency (filtered LFP signal in the γ-band, lower panel) range displayed by animal models of neurodevelopmental disorders. **(c)** Stability of firing fields of place cells (PC) responsible for encoding spatial information is altered in mouse models of schizophrenia. **(d)** Genes associated with neurodevelopmental disorders that regulate the structure and function of local microcircuits illustrated in (a). Disruption of E/I balance during development can induce neural assembly destabilization and circuit reorganization through developmental plasticity. The degree of rearrangement in neural circuits, i.e. developmental plasticity index, varies as a function of the temporal onset in E/I imbalance during postnatal development (P: postnatal day in mouse development).

References and recommended reading

1. Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, et al.: **De novo mutations in schizophrenia implicate synaptic networks**. *Nature* 2014, **506**:179-184.

2. Marín O: **Developmental timing and critical windows for the treatment of psychiatric disorders**. *Nat Med* 2016, **22**:1229-1238.

3. Owen MJ, O'Donovan MC: **Schizophrenia and the neurodevelopmental continuum: Evidence from genomics**. *World Psychiatry* 2017, **16**:227-235.

4. Kaiser T, Feng G: **Modeling psychiatric disorders for developing effective treatments**. *Nat Med* 2015, **21**:979-988.

5. Meyer-Lindenberg AS, Olsen RK, Kohn PD, Brown T, Egan MF, Weinberger DR, Berman KF: **Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia**. *Arch Gen Psychiatry* 2005, **62**:379-386.

6. Lawrie SM, Buechel C, Whalley HC, Frith CD, Friston KJ, Johnstone EC: **Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations**. *Biol Psychiatry* 2002, **51**:1008-1011.

7. Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA: **Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia**. *Nature* 2010, **464**:763-767.

8. Mukai J, Tamura M, Fenelon K, Rosen AM, Spellman TJ, Kang R, MacDermott AB, Karayiorgou M, Gordon JA, Gogos JA: **Molecular substrates of altered axonal growth and brain connectivity in a mouse model of schizophrenia**. *Neuron* 2015, **86**:680-695.

9. Tamura M, Mukai J, Gordon JA, Gogos JA: **Developmental inhibition of Gsk3 rescues behavioral and neurophysiological deficits in a mouse model of schizophrenia predisposition**. *Neuron* 2016, **89**:1100-1109.

10. Courchesne E, Pierce K: **Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection**. *Curr Opin Neurobiol* 2005, **15**:225-230.

11. Poot M: **Connecting the CNTNAP2 networks with neurodevelopmental disorders**. *Mol Syndromol* 2015, **6**:7-22.

12. Liska A, Bertero A, Gomolka R, Sabbioni M, Galbusera A, Barsotti N, Panzeri S, Scattoni ML, Pasqualetti M, Gozzi A: **Homozygous loss of autism-risk gene CNTNAP2 results in reduced local and long-range prefrontal functional connectivity**. *Cereb Cortex* 2017, **10.1093/cercor/bhx022**.

13. Haberl MG, Zerbi V, Veltien A, Ginger M, Heerschap A, Frick A: **Structural-functional connectivity deficits of neocortical circuits in the Fmr1 (-/y) mouse model of autism**. *Sci Adv* 2015, **1**:e1500775.

14. La Fata G, Gartner A, Dominguez-Iturza N, Dresselaers T, Dawitz J, Poorthuis RB, Averna M, Himmelreich U, Meredith RM, Achsel T, et al.: **FMRP regulates multipolar to bipolar transition affecting neuronal migration and cortical circuitry**. *Nat Neurosci* 2014, **17**:1693-1700.

15. Huang WC, Chen Y, Page DT: **Hyperconnectivity of prefrontal cortex to amygdala projections in a mouse model of macrocephaly/autism syndrome**. *Nat Commun* 2016, **7**:13421.

16. Oguro-Ando A, Rosensweig C, Herman E, Nishimura Y, Werling D, Bill BR, Berg JM, Gao F, Coppola G, Abrahams BS, et al.: **Increased CYFIP1 dosage alters cellular and dendritic morphology and dysregulates mTOR**. *Mol Psychiatry* 2015, **20**:1069-1078.

17. Marín O: **Interneuron dysfunction in psychiatric disorders**. *Nat Rev Neurosci* 2012, **13**:107-120.

18. Krishnan K, Wang BS, Lu J, Wang L, Maffei A, Cang J, Huang ZJ: **MeCP2 regulates the timing of critical period plasticity that shapes functional connectivity in primary visual cortex**. *Proc Natl Acad Sci USA* 2015, **112**:E4782-4791.

19. Lu H, Ash RT, He L, Kee SE, Wang W, Yu D, Hao S, Meng X, Ure K, Ito-Ishida A, et al.: **Loss and gain of MeCP2 cause similar hippocampal circuit dysfunction that is rescued by deep brain stimulation in a Rett syndrome mouse model**. *Neuron* 2016, **91**:739-747.

20. Kwon CH, Luikart BW, Powell CM, Zhou J, Matheny SA, Zhang W, Li Y, Baker SJ, Parada LF: **Pten regulates neuronal arborization and social interaction in mice**. *Neuron* 2006, **50**:377-388.

21. Vogt D, Cho KKA, Lee AT, Sohal VS, Rubenstein JLR: **The parvalbumin/somatostatin ratio is increased in Pten mutant mice and by human PTEN ASD alleles**. *Cell Reports* 2015, **11**:944-956.

22. Chung DW, Fish KN, Lewis DA: **Pathological Basis for Deficient Excitatory Drive to Cortical Parvalbumin Interneurons in Schizophrenia**. *Am J Psychiatry* 2016, **173**:1131-1139.

23. Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA: **Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia**. *Cereb Cortex* 2002, **12**:1063-1070.

24. Uhlhaas PJ, Singer W: **Abnormal neural oscillations and synchrony in schizophrenia**. *Nat Rev Neurosci* 2010, **11**:100-113.

25. Uhlhaas PJ, Linden DE, Singer W, Haenschel C, Lindner M, Maurer K, Rodriguez E: **Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia**. *J Neurosci* 2006, **26**:8168-8175.

26. Hirano S, Hirano Y, Maekawa T, Obayashi C, Oribe N, Kuroki T, Kanba S, Onitsuka T: **Abnormal neural oscillatory activity to speech sounds in schizophrenia: a magnetoencephalography study**. *J Neurosci* 2008, **28**:4897-4903.

27. Sun L, Castellanos N, Grutzner C, Koethe D, Rivolta D, Wibral M, Kranaster L, Singer W, Leweke MF, Uhlhaas PJ: **Evidence for dysregulated high-frequency oscillations during sensory processing in medication-naive, first episode schizophrenia**. *Schizophr Res* 2013, **150**:519-525.

28. Andreou C, Nolte G, Leicht G, Polomac N, Hanganu-Opatz IL, Lambert M, Engel AK, Mulert C: **Increased Resting-State Gamma-Band Connectivity in First-Episode Schizophrenia**. *Schizophr Bull* 2015, **41**:930-939.

29. Tada M, Nagai T, Kirihara K, Koike S, Suga M, Araki T, Kobayashi T, Kasai K: **Differential Alterations of Auditory Gamma Oscillatory Responses Between Pre-Onset High-Risk Individuals and First-Episode Schizophrenia**. *Cereb Cortex* 2016, **26**:1027-1035.

30. Crabtree GW, Park AJ, Gordon JA, Gogos JA: **Cytosolic Accumulation of L-Proline Disrupts GABA-Ergic Transmission through GAD Blockade**. *Cell Reports* 2016, **17**:570-582.

31. Polepalli JS, Wu H, Goswami D, Halpern CH, Sudhof TC, Malenka RC: **Modulation of excitation on parvalbumin interneurons by neuroligin-3 regulates the hippocampal network**. *Nat Neurosci* 2017, **20**:219-229.

32. del Pino I, Garcia-Frigola C, Dehorter N, Brotons-Mas JR, Alvarez-Salvado E, Martinez de Lagran M, Ciceri G, Gabaldon MV, Moratal D, Dierssen M, et al.: **Erbb4 deletion from fast-spiking interneurons causes schizophrenia-like phenotypes**. *Neuron* 2013, **79**:1152-1168.

33. del Pino I, Brotons-Mas JR, Marques-Smith A, Marighetto A, Frick A, Marín O, Rico B: **Abnormal wiring of CCK+ basket cells disrupts spatial information coding**. *Nat Neurosci* 2017, **20**:784-792.

34. Zaremba JD, Diamantopoulou A, Danielson NB, Grosmark AD, Kaifosh PW, Bowler JC, Liao Z, Sparks FT, Gogos JA, Losonczy A: **Impaired hippocampal place cell dynamics in a mouse model of the 22q11.2 deletion**. *Nat Neurosci* 2017, **20**:1612-1623.

35. Chen LY, Jiang M, Zhang B, Gokce O, Sudhof TC: **Conditional deletion of all neurexins defines diversity of essential synaptic organizer functions for neurexins**. *Neuron* 2017, **94**:611-625 e614.

36. Hammer M, Krueger-Burg D, Tuffy LP, Cooper BH, Taschenberger H, Goswami SP, Ehrenreich H, Jonas P, Varoqueaux F, Rhee JS, et al.: **Perturbed hippocampal synaptic inhibition and gamma-oscillations in a Neuroligin-4 knockout mouse model of autism**. *Cell Reports* 2015, **13**:516-523.

37. Fazzari P, Paternain AV, Valiente M, Pla R, Lujan R, Lloyd K, Lerma J, Marín O, Rico B: **Control of cortical GABA circuitry development by Nrg1 and ErbB4 signalling**. *Nature* 2010, **464**:1376-1380.

38. Selimbeyoglu A, Kim CK, Inoue M, Lee SY, Hong ASO, Kauvar I, Ramakrishnan C, Fenno LE, Davidson TJ, Wright M, et al.: **Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice**. *Sci Transl Med* 2017, **9**.

39. Cho KK, Hoch R, Lee AT, Patel T, Rubenstein JL, Sohal VS: **Gamma rhythms link prefrontal interneuron dysfunction with cognitive inflexibility in Dlx5/6(+/-) mice**. *Neuron* 2015, **85**:1332-1343.

40. Hamm JP, Peterka DS, Gogos JA, Yuste R: **Altered Cortical Ensembles in Mouse Models of Schizophrenia**. *Neuron* 2017, **94**:153-167 e158.

41. Peixoto RT, Wang W, Croney DM, Kozorovitskiy Y, Sabatini BL: **Early hyperactivity and precocious maturation of corticostriatal circuits in Shank3B(-/-) mice**. *Nat Neurosci* 2016, **19**:716-724.

42. Ahmari SE, Spellman T, Douglass NL, Kheirbek MA, Simpson HB, Deisseroth K, Gordon JA, Hen R: **Repeated cortico-striatal stimulation generates persistent OCD-like behavior**. *Science* 2013, **340**:1234-1239.

43. Zhou Y, Kaiser T, Monteiro P, Zhang X, Van der Goes MS, Wang D, Barak B, Zeng M, Li C, Lu C, et al.: **Mice with Shank3 mutations associated with ASD and schizophrenia display both shared and distinct defects**. *Neuron* 2016, **89**:147-162.

44. Chen YC, Kuo HY, Bornschein U, Takahashi H, Chen SY, Lu KM, Yang HY, Chen GM, Lin JR, Lee YH, et al.: **Foxp2 controls synaptic wiring of corticostriatal circuits and vocal communication by opposing Mef2c**. *Nat Neurosci* 2016, **19**:1513-1522.

45. Chadman KK, Gong S, Scattoni ML, Boltuck SE, Gandhy SU, Heintz N, Crawley JN: **Minimal aberrant behavioral phenotypes of neuroligin-3 R451C knockin mice**. *Autism Res* 2008, **1**:147-158.

46. Rothwell PE, Fuccillo MV, Maxeiner S, Hayton SJ, Gokce O, Lim BK, Fowler SC, Malenka RC, Sudhof TC: **Autism-associated neuroligin-3 mutations commonly impair striatal circuits to boost repetitive behaviors**. *Cell* 2014, **158**:198-212.

47. Tian D, Stoppel LJ, Heynen AJ, Lindemann L, Jaeschke G, Mills AA, Bear MF: **Contribution of mGluR5 to pathophysiology in a mouse model of human chromosome 16p11.2 microdeletion**. *Nat Neurosci* 2015, **18**:182-184.

48. Platt RJ, Zhou Y, Slaymaker IM, Shetty AS, Weisbach NR, Kim JA, Sharma J, Desai M, Sood S, Kempton HR, et al.: **Chd8 mutation leads to autistic-like behaviors and impaired striatal circuits**. *Cell Reports* 2017, **19**:335-350.

49. Graybiel AM: **Habits, rituals, and the evaluative brain**. *Annu Rev Neurosci* 2008, **31**:359-387.

50. Zahir F, Firth HV, Baross A, Delaney AD, Eydoux P, Gibson WT, Langlois S, Martin H, Willatt L, Marra MA, et al.: **Novel deletions of 14q11.2 associated with developmental delay, cognitive impairment and similar minor anomalies in three children**. *J Med Genet* 2007, **44**:556-561.

51. Katayama Y, Nishiyama M, Shoji H, Ohkawa Y, Kawamura A, Sato T, Suyama M, Takumi T, Miyakawa T, Nakayama KI: **CHD8 haploinsufficiency results in autistic-like phenotypes in mice**. *Nature* 2016, **537**:675-679.

52. Durak O, Gao F, Kaeser-Woo YJ, Rueda R, Martorell AJ, Nott A, Liu CY, Watson LA, Tsai LH: **Chd8 mediates cortical neurogenesis via transcriptional regulation of cell cycle and Wnt signaling**. *Nat Neurosci* 2016, **19**:1477-1488.

53. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S: **The nature of dopamine dysfunction in schizophrenia and what this means for treatment**. *Arch Gen Psychiatry* 2012, **69**:776-786.

54. Choi SJ, Mukai J, Kvajo M, Xu B, Diamantopoulou A, Pitychoutis PM, Gou B, Gogos JA, Zhang H: **A Schizophrenia-Related Deletion Leads to KCNQ2-Dependent Abnormal Dopaminergic Modulation of Prefrontal Cortical Interneuron Activity**. *Cereb Cortex* 2017:1-17.

55. Kim IH, Rossi MA, Aryal DK, Racz B, Kim N, Uezu A, Wang F, Wetsel WC, Weinberg RJ, Yin H, et al.: **Spine pruning drives antipsychotic-sensitive locomotion via circuit control of striatal dopamine**. *Nat Neurosci* 2015, **18**:883-891.

56. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY: **Reward processing in autism**. *Autism Res* 2010, **3**:53-67.

57. Bariselli S, Tzanoulinou S, Glangetas C, Prevost-Solie C, Pucci L, Viguie J, Bezzi P, O'Connor EC, Georges F, Luscher C, et al.: **SHANK3 controls maturation of social reward circuits in the VTA**. *Nat Neurosci* 2016, **19**:926-934.

58. Krishnan V, Stoppel DC, Nong Y, Johnson MA, Nadler MJ, Ozkaynak E, Teng BL, Nagakura I, Mohammad F, Silva MA, et al.: **Autism gene Ube3a and seizures impair sociability by repressing VTA Cbln1**. *Nature* 2017, **543**:507-512.

59. Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ: **Children and adolescents with autism exhibit reduced MEG steady-state gamma responses**. *Biol Psychiatry* 2007, **62**:192-197.

60. Tomchek SD, Dunn W: **Sensory processing in children with and without autism: a comparative study using the short sensory profile**. *Am J Occup Ther* 2007, **61**:190-200.

61. Orefice LL, Zimmerman AL, Chirila AM, Sleboda SJ, Head JP, Ginty DD: **Peripheral mechanosensory neuron dysfunction underlies tactile and behavioral deficits in mouse models of ASDs**. *Cell* 2016, **166**:299-313.

62. Wells MF, Wimmer RD, Schmitt LI, Feng G, Halassa MM: **Thalamic reticular impairment underlies attention deficit in Ptchd1(Y/-) mice**. *Nature* 2016, **532**:58-63.

63. Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, Bjornsdottir G, Walters GB, Jonsdottir GA, Doyle OM, et al.: **CNVs conferring risk of autism or schizophrenia affect cognition in controls**. *Nature* 2014, **505**:361-366.

Papers of particular interest, published within the period of review, have been highlighted as:

- ● of special interest
- ●● of outstanding interest

● Mukai et al., Neuron 2015

This study links defects in hippocampal-prefrontal synchrony observed in Df(16)A(+/-) mice, which model the 22q11.2 deletion, to aberrant connectivity between these regions. The authors provide evidence suggesting that this phenotype is at least partially due to loss of Zdhhc8, a regulator of axonal growth.

●● Tamura et al., Neuron 2016

The authors report that the use of pharmacological Gsk3 antagonists during postnatal development can rescue axonal outgrowth in Df(16)A(+/-) mice, which model the 22q11.2 deletion. This treatment also restore functional and behavioral impairments observed in Df(16)A(+/-) mice. This study highlights the potential of early pharmacological interventions for restoring neural circuit dysfunction in neurodevelopmental disorders.

●● Peixoto et al., Nat Neurosci 2016

This paper identifies a critical window for the development of cortico-striatal circuits in which the connections between cortical and striatal neurons are highly sensitive to activity. The authors also report that cortical hyperactivity in Shank3 mouse mutants during this critical period lead to aberrant corticostriatal hyperconnectivity.

●● Zhou et al., Neuron 2016

The authors reveal dysfunctions in cortical and striatal circuits that are unique or shared between mouse lines harboring different Shank3 mutations associated to either ASD or schizophrenia. This study provides an excellent example of how different mutations on the same gene may give rise to distinct behavioral outcomes by disrupting neural circuit function in different ways.

●● del Pino et al., Nat Neurosci 2017

This study links developmental defects in the wiring of CCK+ basket cells to aberrant spatial information coding and behavioral deficits in spatial learning and memory in adult mice.

● Chen et al., Neuron 2017

Using conditional mutants that delete all neurexins, this study reveals that the function of neurexins in the organisation of synapses is context-dependent. Disruption of neurexins seem to cause dramatically different phenotypes in diverse neural circuits.

● Selimbeyoglu et al., Sci Transl Med 2017

This manuscript reveals that acute modulation of adult cortical circuits using optogenetics is sufficient to restore behavioral abnormalities in a mouse model of syndromic autism.

● Birey et al., Nature 2017

Together with Bagley and colleagues, this study reports a protocol for the generation of human organoids containing both excitatory and inhibitory cortical cells by fusing patterned mini-organoids. Using this method, the authors reveal that defects in the migration of interneurons may contribute to neural circuit abnormalities found in Timothy syndrome.

● Bagley et al., Nat Methods 2017

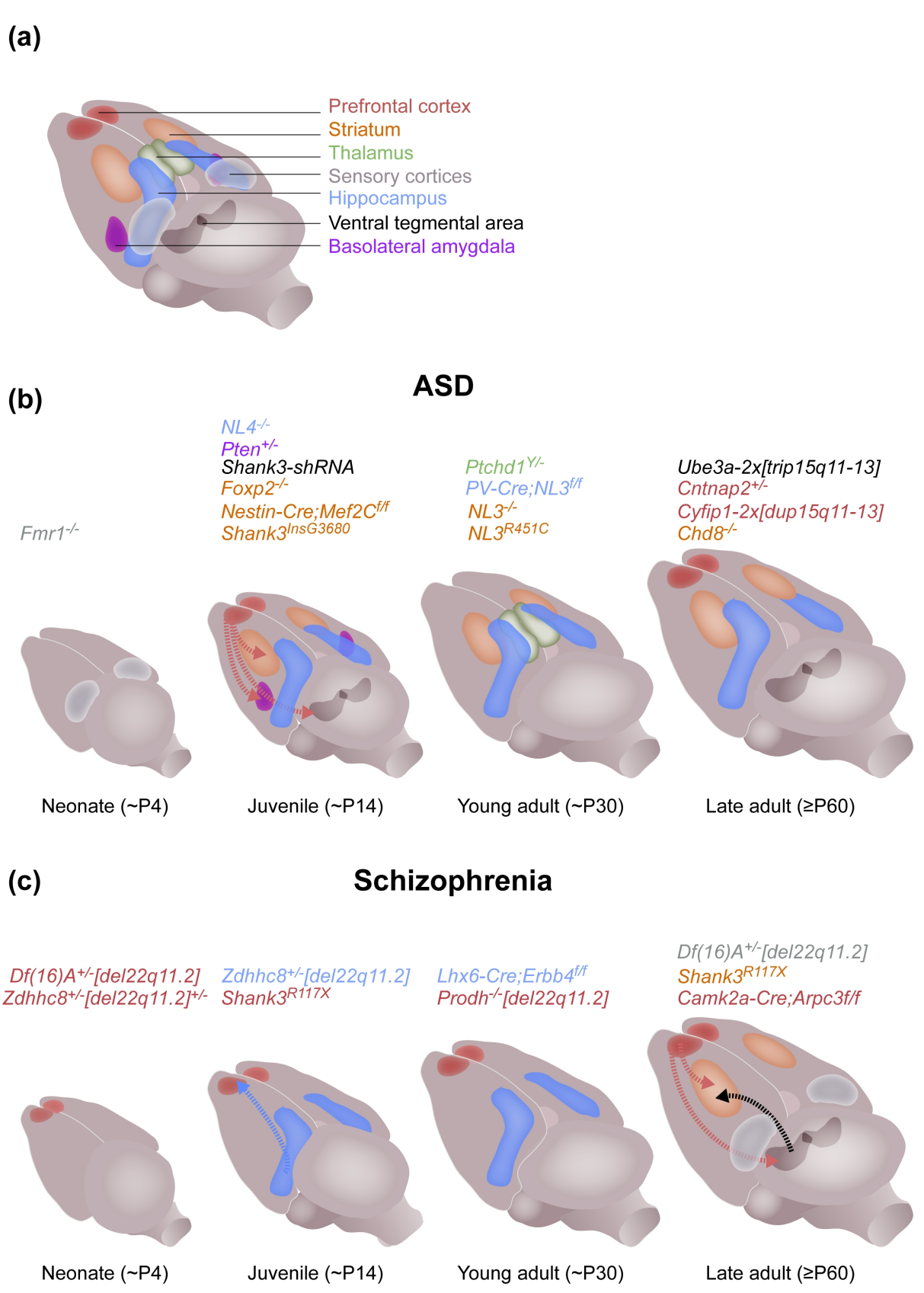
Together with Birey and colleagues, this study reports a protocol for the generation of human organoids containing both excitatory and inhibitory cortical cells by fusing patterned mini-organoids.

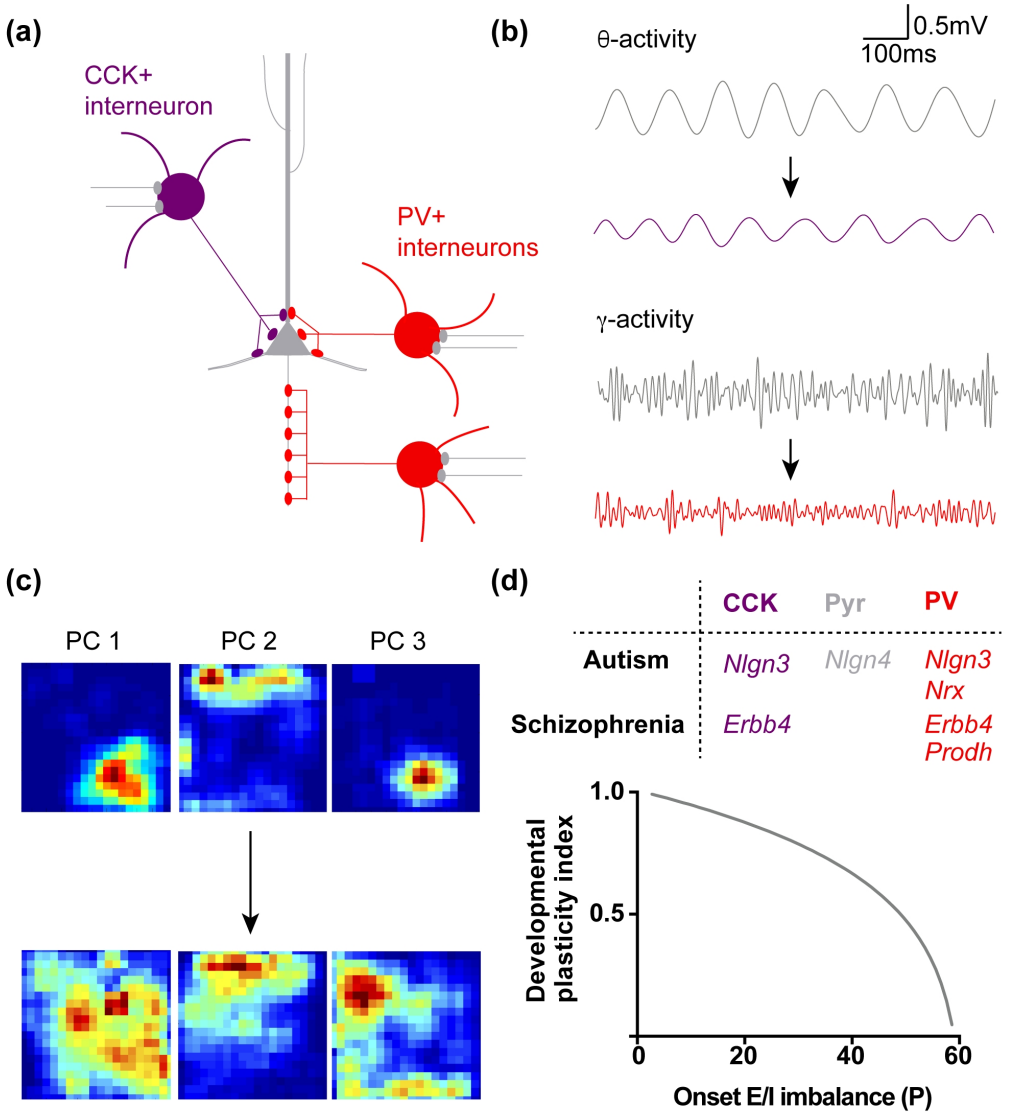
●● Orefice et al., Cell 2016

This study uses several mouse models of ASD to identify defects in primary sensory neurons and spinal cord neural circuits as the most likely sources of aberrant tactile sensitivity in autism.

●● Kim et al., Nature Neuroscience 2015

The authors show that perturbation of actin-cytoskeleton dynamics in prefrontal cortex networks leads to increased neuronal excitability and striatal hyperdopaminergia. The authors provide experimental evidence linking unrelated pathological features observed in schizophrenia.


(a)
Prefrontal cortex
Striatum
Thalamus
Sensory cortices
Hippocampus
Ventral tegmental area
Basolateral amygdala
(b)
ASD
Fmr1-/-
NL4-/-
Pten+/-
Shank3-shRNA
Foxp2-/-
Nestin-Cre;Mef2Cf/f
Shank3InsG3680
Ptchd1Y/-
PV-Cre;NL3f/f
NL3-/-
NL3R451C
Ube3a-2x[trip15q11-13]
Cntnap2+/-
Cyfip1-2x[dup15q11-13]
Chd8-/-
Neonate (~P4)
Juvenile (~P14)
Young adult (~P30)
Late adult (≥P60)
(c)
Schizophrenia
Df(16)A+/-[del22q11.2]
Zdhhc8+/-[del22q11.2]+/-
Zdhhc8+/-[del22q11.2]
Shank3R117X
Lhx6-Cre;Erbb4f/f
Prodh-/-[del22q11.2]
Df(16)A+/-[del22q11.2]
Shank3R117X
Camk2a-Cre;Arpc3f/f
Neonate (~P4)
Juvenile (~P14)
Young adult (~P30)
Late adult (≥P60)


(a)
CCK+
interneuron
PV+
interneurons
(b)
θ-activity
0.5mV
100ms
γ-activity
(c)
PC 1
PC 2
PC 3
(d)
CCK
Pyr
PV
Autism
Nlgn3
Nlgn4
Nlgn3
Nrx
Schizophrenia
Erbb4
Erbb4
Prodh
1.0
0.5
Developmental
plasticity index
0
20
40
60
Onset E/I imbalance (P)